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Process for the preparation of cosmetic formulations

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In the preparation of emulsions, suspensions and dispersions which are delivered to the end consumer, it is desirable to obtain products which are stable for an extended period, do not tend to separate out and in which at the same time the added active ingredients retain their activity. The stability of mixtures is achieved in conventional products by the addition of additives, such as, for example, emulsifiers, surfactants or the like. In order to prevent decomposition of the contents and to hinder a decrease in the activity of active ingredients present, oxidation stabilisers, free-radical scavengers, bactericides and other additives, for example, are added. Various of these additives may result in irritation or allergies in the case of sensitive users.

In order to stabilise active ingredients, it is in many cases not the active ingredient itself that is used, but instead one of its more stable derivatives, which then decomposes at the site of action and liberates the active ingredient. This is of course afflicted with the problem that the derivative behaves differently to the actual active ingredient in any prior transport or metabolism processes which are necessary.

A further problem in the preparation of the above-mentioned mixtures is homogeneous mixing of the individual substances in each volume element of the mixture as a whole.

In order to prepare cosmetic formulations, simple stirred vessels with various types of stirrer are frequently used. Depending on the stirrer type (for example anchor, propeller, inclined-blade, disc, EKATO multistage impulse countercurrent stirrers or EKATO Mizer disc), different shear forces occur in the stirred vessels depending on the location in the stirred vessel. The same applies to the temperature distribution and energy input into the formulation, which means that shear forces, temperature and introduced energy are not "uniformly" distributed in the batch vessel, and consequently the build-up of the resultant formulation is adversely affected. In concrete terms, this means that, for example, emulsions may form in which the emulsified phase has very different particle sizes, or the active-ingredient distribution in a prepared product is non-uniform.

The object of the present invention is therefore to provide a process which gives mixed products which have a homogeneous distribution of all

components in the mixture as a whole and at the same time have a homogeneous distribution of the particle or droplet size. A further object of the invention is to provide a process for the preparation of cosmetic or pharmaceutical formulations by means of which the use of emulsifiers, surfactants, stabilisers, oxidation stabilisers, free-radical scavengers, bactericides and other additives can be restricted or by means of which, in the ideal case, their use can be omitted entirely. A further object of the invention is to provide a process by means of which cosmetic or pharmaceutical formulations can be prepared in very small amounts immediately before their use.

The object according to the invention is achieved by a process for the preparation of cosmetic or pharmaceutical formulations immediately before use, characterised in that two or more liquid components from separate stock chambers are mixed with one another by passing them through a micromixer.

In order to carry out the process according to the invention, two or more components in liquid form, if necessary after warming, from separate stock chambers are passed through a micromixer for mixing.

The mixing can take place by passing the components in liquid form, if necessary after warming, from separate stock chambers through a temperature-controlled micromixer and if necessary continuing stirring for cooling.

The process for the preparation of cosmetic or pharmaceutical formulations in the form of emulsions immediately before use can be carried out by passing one or more liquid component(s) with one or more natural, synthetic or semi-synthetic oil(s) from separate stock chambers through a micromixer, during which they are mixed with one another.

The object according to the invention is also achieved by a process for the preparation of cosmetic formulations in the form of emulsions immediately before use, characterised in that a fat phase consisting of one or more natural, synthetic or semi-synthetic oil(s) and one or more fat(s) which is

to the pressure prevailing in the stock chambers, an adequate pressure is built up in the micromixer to force the components through the channels with intensive mixing and formation of a liposome-containing formulation.

The present invention is also achieved by means of lotions or solution, emulsions, gels and creams which can be prepared by the process according to the invention.

For certain formulations, uniform mixing, a constant temperature and uniform input of energy even at the micro-level, are important. It has now been found that the use of micromixers enables the preparation of mixtures in the form of emulsions, suspensions and dispersions, lotions, solutions gels and creams in which all contents are uniformly distributed, even in extremely small volume parts. In contrast to a large-volume stirred reactor, it is possible to prepare these mixtures under uniform temperature conditions, even at the micro-level, since no temperature gradient forms in the thin, optionally laminate-like channels, in particular if the micromixer has a temperature-controllable design. Furthermore, the input of energy is the same in each volume part, i.e. even in the smallest. It has also been found that emulsions having a significantly more homogeneous droplet size distribution can be prepared than in a stirred vessel. Owing to the multiple shear conditions of the communicating channels in the micromixer, droplet sizes in the micro-range are inevitably specified, so that microemulsions are obtained, which could only be prepared in a very complex manner in a stirred vessel. The use of a micromixer is therefore suitable for the preparation of very fine homogeneous formulations.

Suitable for carrying out the process according to the invention are micromixers and associated connection and sealing systems which are described in the patent applications DE 1 95 11 603, DE 1 97 46 583, DE 1 97 46 584, DE 19746585 and DE 1 98 54 096, and modifications thereof that are evident to the person skilled in the art. Suitable micromixers may consist of suitable metallic, ceramic or polymeric materials or of silicon.

Problematic formulations in the W/O area are emulsions, in particular those having high contents of vegetable triglycerides. Emulsions without

stabilising waxes are frequently distinguished by inadequate long-term viscosity constancy, and O/W lotions are generally more difficult to stabilise than creams. These emulsions can therefore be prepared particularly well using micromixers. It is of particular advantage here than the use of micromixers enables particularly small amounts to be prepared, which can advantageously be prepared in situ, i.e. directly before use.

Microemulsions are thermodynamically stable if, owing to extremely low interfacial energy, they are formed spontaneously, i.e. without the supply of external mechanical energy. The droplet diameters are significantly smaller than in the case of macroemulsions; they are in the range 10-30 nm (nanometers), i.e. below the wavelength of visible light. Microemulsions are therefore colloidally disperse, optically transparent systems. According to POHLER, certain concentration ranges of the oil and water phases and of the emulsifiers and auxiliaries must be observed for the formulation of microemulsions:

Surfactants (usually nonionic surfactants) 15 - 40%

Mineral oil or vegetable oil 5 - 25%

Polyalcohols 0 - 20%

Water 35 - 65%

The use of micromixers for the preparation of microemulsions enables the use of surfactants to be considerably reduced, enabling the toleration for particularly sensitive skin types to be significantly increased. Stable microemulsions can be prepared using as little as less than 10% by weight of surfactants.

The most important requirements of emulsification equipment are usually adequate and in particular variable emulsification power, sufficient shear or impact forces, fitting-out for uniform treatment of the batch, vacuum device, heating and cooling (14). These problems can be solved in a simple manner in accordance with the invention through the use of suitable micromixers, which ensure specific input of energy in each

volume element and in which intensive mixing takes place in the thin channels with exposure to intensive shear forces.

The use of micromixers furthermore enables very small amounts of the desired cosmetic or pharmaceutical formulations to be prepared immediately before use. This has the advantage that the addition of emulsifiers, suspension aids and dispersion aids in the form of surfactants and other additives, such as, for example, stabilisers, can be greatly restricted or their use can be omitted entirely. It is also possible in this way for active ingredients or additives which are incompatible with one another in a formulation over an extended period not to be mixed with one another until directly before use.

Active ingredients which are only stable in a formulation in the form of a derivative can be initially introduced as such in a separate formulation and not added to the remaining mixture until directly before use. This also enables the user to add various additives, as desired, to small amounts of a base mixture at various points in time. This may be of interest both for pharmaceutical and for cosmetic formulations if different active ingredients are to be applied at different points in time.

Different additives can be added to a cosmetic base formulation for the day than for the night. Additives for the day may be, for example, UV filters, while those for the night may be regenerating additives.

For better understanding and for illustration, examples are given below which fall within the scope of protection of the present invention, but are not suitable for restricting the invention to these examples.

Example 1

Hand and nail cream

	Raw material		INCI	% W/W
A	Paraffin (Art. No. 107162)	(1)	Mineral Oil	2.00
	Arlamol HD	(2)	Isohexadecane	2.00

		Isopropyl palmitate	(3)	Isopropyl Palmitate	3.00
		Soya oil	(4)	Glycine Soya	0.50
		Mirasil DM 350	(5)	Dimethicone	1.00
		Lanette O	(3)	Cetearyl Alcohol	1.00
		Span 60	(2)	Sorbitan Stearate	1.50
		Montanov 68	(6)	Cetearyl Alcohol (and) Cetearyl Glucoside	4.00
		(-) -(α-Bisabolol (Art. No.130170)	(1)	Bisabolol	0.30
	B	Demin. water		Aqua	to 100
		Glycerin, 87% (Art. No.104091)	(1)	Glycerin	10.00
		D-Panthenol	(7)	Panthenol	0.50
		(D+)-Biotin (Art. No.130220)	(1)	Biotin	0.05
		(if desired) preservatives			q.s.
	C	Rhodicare S	(5)	Xanthan Gum	0.30
	If desired:				
	D	Perfume Bianca	(8)	Perfume	0.20

Preparation:

Phases A, B and C are each introduced separately into a stock container and heated to 75°C. The consequently liquid phases B and C are pumped out of the stock containers and passed through a micromixer held at 75°C and mixed. The mixture emerging from the micromixer is subsequently pumped with phase A through a micromixer held at 75°C and homogenised. The resultant emulsion is collected in a stock container and cooled with stirring. At a temperature of about 35°C, the perfume can be added if desired.

Notes:

$pH_{25°C}$ value: 5.5
Viscosity: 43000 mPa.s (Brookfield RVT, spindle C, 5 rpm, Helipath) at 25°C
0.05% of propyl 4-hydroxybenzoate (Merck KGaA, Art. No. 130173),

0.15% of methyl 4-hydroxybenzoate (Merck KGaA, Art. No. 13 0174),
0.30% of Germall 115 (ISP, Frechen)

Procurement sources:

(1) Merck KGaA, Darmstadt
(2) ICI Surfactants, Essen
(3) Henkel KGaA, Düsseldorf
(4) Gustav Hees, Stuttgart
(5) Rhodia, Frankfurt
(6) Seppic, France
(7) BASF, Ludwigshafen
(8) HandR, Holzminden

Example 2

W/0 body-care milk (COLD PREPARATION)

A.	ARLACEL 780	5.0 %
	Paraffin oil, low-viscosity	10.0 %
	Miglyol 812	4.0 %
	ARLAMOL HD	5 0 %
	ARLAMOL E	1.0 %
	Perfume (if desired)	q.s.
B.	Glycerin	2.5 %
	ATLAS G-2330	1.5 %
	Mg $S0_4$	0.5 %
	Demin. water	70.5 %
	Preservative (if desired)	q.s.

Preparation method:

The two phases A and B are each introduced separately into a stock container. After mixing, which can be carried out either by stirring or in small vessels by shaking, the phases are pumped out of the stock containers and passed jointly through a micro-mixer, in which the phases are mixed intensively. The homogeneously mixed milk can be used directly.

Viscosity:

10 000 mPa s (Brookfield LVT Helipath, spindle C, 6 rpm, 1 min.)

Procurement sources:

(1) ICI Surfactants

Example 3

Sun-protection milk (W/S) (water in silicone)

A	Eusolex 2292 (Art. No. 5382)	(1)	2.00
	DC 1401	(2)	10.00
	DC 3225 C	(2)	10.00
	Dow Corning 344	(2)	10.00
			q.s.
B	Eusolex 232 (Art. No. 5372)	(1)	2.00
		Tris(hydroxymethyl)-	
		(1)	0.88
	aminomethane (Art. No. 8386)		
		Sodium chloride (Art.	
	No. 6400)	(1)	2.00
		Glycerin (Art.-Nr. 4093)	
		(1)	5.00
		Preservative (if	
	desired.)		q.s.
		Water,	
	demineralised		to 100.00

Preparation:

In order to prepare phase B, tris(hydroxymethyl)aminomethane for neutralisation of Eusolex 232 is dissolved in water in a stock vessel, and Eusolex 232 is added. After complete dissolution, the remaining raw materials of phase B are added. The components of phase A are pre-mixed in a second stock vessel.

In order to prepare the sun-protection milk, the two phases are, for mixing, pumped jointly with the aid of a pump through a micromixer connected via thin connecting tubes.

Notes

Viscosity 22,800 mPas (Brookfield RVT, spindle C, 10 rpm) at 25 'C
Samples contain the following as preservatives:
0.05% of propyl 4-hydroxybenzoate (Merck Art. No. 7427)
0.17 % of methyl 4-hydroxybenzoate, sodium salt (Merck Art. No. 6756)

Procurement sources:

(1) E. Merck, Darmstadt
(2) Dow Corning, Düsseldorf

Example 4

Transparent microemulsion

Trade name	INCI	% by weight
Eumulgin B2	Ceteareth-20	19.5
Cetiol RE	PEG-7 Glyceryl Cocoate	20.0
Uniphen P-23	Phenoxyethanol + Methyl-/ Ethyl-/Propyl-/Butylparaben	0.3
Mineral oil	Mineral Oil	5.0
Glycerin	Glycerin	20.0
Water, demin..	Water	35.2

Preparation:

1. Eumulgin B2, Cetiol HE, Uniphen P-23 and the paraffin oil are introduced into a stock vessel, melted with mixing and heated to about 95°C-105°C.

2. Water and the glycerin are combined and likewise heated to about 95°C-100°C. Increase the amount of water by 3%.

3. The water phase and the fat phase are pumped through a micromixer for intensive mixing. The resultant microemulsion gel stirs for cooling.

Alternatively, it is possible to pass the microemulsion gel through a further, cooled micromixer whose exit channels have a broader cross section, thus preventing blockage of the channels and suppressing the formation of air bubbles in the gel.

At a temperature at which the microemulsion gel is still just pourable, it is transferred into the primary packaging.

Example 5

Sun-protection gel (emulsifier-free)
SPF 3.21 UVA PF 2.5 (sun protection factor, Diffey Method)

			% by weight
A	Eusolex 2292 (Art. No. 105382)	(1)	1.000
	Luvitol EHO	(2)	9.000
	Dow Corning 200 (100 cs)	(3)	2.000
	Antaron V-220	(4)	2.000
	Jojoba oil	(5)	5.000
	DL-α-Tocopherol acetate (Art. No. 500952)	(1)	0.500
B	Tris(hydroxymethyl)aminomethane (Art. No. 108386)	(1)	0.700
	Water, demineralised		14.300
C	Pemulen TR-1	(6)	0.600
	Preservative (if desired)	(1)	q.s.
	Water, demineralised		to 100. 000
D	Aloe Vera Gel 1: 10	(7)	1.000

Preparation:

For phase C, homogeneously disperse the Pemulen TR-1 in water, add preservative and pre-swell. Introduce phase B into phase C with homogenisation. Dissolve phase A with heating and add slowly with homogenisation. Add phase D at 35°C and again homogenise.

Notes:

Viscosity 67,000 mPas (Brookfield RVT, spindle C, 5 rpm) at 25°C
$PH_{25°C}$ = 6.9
As preservative, 1.0% of phenoxyethanol (Merck Art. No. 807291) can be added.

Procurement sources

(1) Merck KGaA, Darmstadt
(2) BASF, Ludwigshafen
(3) Dow Corning, Düsseldorf
(4) GAF, Frechen
(5) Henry Lamotte, Bremen
(6) Goodrich, Neuss
(7) Rahn, Maintal

Example 6

In situ *W/O/W* super-moisturising cream

Composition:

	W/W
A	
'Brij 721	2.0
Brij 72	3.0
Arlacel P135	0.5
Arlamol E	5.0
Arlamol HD	4.0
Vitamin E acetate	1.0
Laurex CS	1.0
Stearic acid	1.5
Mirasil DM 100	1.0
B	
1.2-Propylene glycol	4.0
Allantoin	0.2
Urea	0.5
Water	74.4
C	
Germaben II	1.0

D. (if desired)

Perfume L94-5770 0.1

Preparation:

1. A and B are warmed to a temperature of 75°C in separate stock containers.
2. Before the emulsion is prepared, C is added to B.
3. The phases A and B/C are mixed intensively by pumping them through a micromixer held at 75°C.
4. The resultant emulsion is collected in a stock vessel.
5. If desired, D is added after cooling to a temperature below 35°C.
6. Further cooling to room temperature is carried out with gentle stirring.

Notes:

Viscosity 43,000 mPa.s (Brookfield LVT T-bar spindle, E, rpm 6, 1 min.)

Example 7

W/O/W face moisturiser
(two-step preparation)

Composition:

Primary emulsion W/O

		% W/W
A.	Arlacel 1M0	3.3
	Arlacel 2064	3.0
	Arlamol HD	15.0
	Arlamol` M812	14.0
B	Water	63.7
	Germaben II	1.0

Secondary emulsion W/O/W

A.	Primary emulsion W/O	50.0
B.	'Arlatone 2121	5.0
	Water	44.1
	Keltrol	0.4
C.	Germaben II	0.5

Preparation:

Primary emulsion W/O

1. B is slowly added to A with vigorous stirring.
2. The resultant emulsion is homogenised for a further 5 minutes.

Secondary emulsion W/O/W

1. The composition indicated under B with the exception of Keltrol is warmed to a temperature of 80°C. Keltrol is dispersed in the initially introduced composition with stirring at constant temperature.
   The two separately prepared compositions A and B are mixed in a micromixer as described above.
2. C is added to the emulsion cooled to a temperature below 40°C.
3. The mixture is cooled to room temperature with gentle stirring..

Notes::

Viscosity 16,000 mPa.s (Brookfield LVT, T-) spindle D, rpm 6, min.)